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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,929	01/30/2004	Patrick A. Dreyfus	0508-1063-1	3957

466 7590 10/16/2006

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,929	DREYFUS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01/30/2004; 11/15/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Claims 1-7 are pending in the instant application.

37 C.F.R. § 1.98

The information disclosure statement filed 30 January, 2004, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

Claims 1-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

Claim 1 is vague and indefinite for reciting the phrase cells "loaded with a therapeutic agent" since the claim fails to clearly set forth the nature of the modification to the monocyte-derived cells and the therapeutic or diagnostic agent being expressed. For instance, how are the monocytes "loaded". Are they subject to transduction with a particular gene therapy vector encoding the protein of interest? Are the molecules of interest introduced through some other mechanism? How have the monocyte-derived cells been modified so they are "loaded" with the compound of interest?

Claim 3 is vague and indefinite for referencing a corrective

agent comprising a "chemical product". This term fails to impart any meaningful structural limitations into the claim language. Applicants should clearly and unambiguously identify the structure of the chemical product (i.e., a polypeptide). Appropriate amendment of the claim language is required.

The reference to "infection of the central nervous system" is vague and indefinite since it fails to identify the infectious agent. For instance, is the infection due to a viral, bacterial, parasitic, or fungal infection? What is the actual invading pathogen? It is imperative that these criteria be clearly set forth so the skilled artisan can accurately determine the metes and bounds of the patent protection desired.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broadly directed toward a method of treating any sundry central nervous system (CNS) lesion in a patient through the administration of exogenous monocyte-derived cells that have been loaded with a therapeutic or

diagnostic agent. The cells also have the properties of mobilizing toward the site of the lesion.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the identification of suitable therapeutic or diagnostic agents that can be effectively "loaded" into the monocyte of interest. The claims encompass the treatment of any CNS lesion irrespective of the disease or cause. These lesions can be the result of a stroke, Alzheimer's disease, Parkinson's disease, or any one of a number of other different CNS pathologies. The cause and pathology of any given lesion will vary considerably. Moreover, the precise basis for many CNS pathologies remains to be elucidated. Thus, it is not readily manifest to the skilled artisan which molecules would reasonably be expected to provide a therapeutic effect in any given CNS disorder. The disclosure fails to identify suitable "therapeutic agents" and fails to set forth the salient structural and functional characteristics of these compounds.

2) The disclosure fails to teach the skilled artisan how to properly "load" monocytes with the drug, growth factor, nucleic acid, or chemical of interest. The broadly recited claims encompass the administration of various compounds including proteins, drugs, chemicals, or diagnostic agents. However, the disclosure fails to provide any guidance pertaining to the methods that can be utilized to load said monocytes. How are the compounds of interest introduced into monocytes? How does the skilled artisan prevent these compounds from leaking out before the monocyte reaches the tissue of interest?

3) The disclosure fails to provide adequate guidance pertaining to the ability to target "loaded" monocytes to the tissue of interest. No guidance is provided for the skilled artisan that would lead to the reproducible targeting of monocytes to the various tissues of interest. As noted *supra*, the claims encompass the treatment of any given CNS pathology. Lesions of the CNS can be caused by any one of a number of different disorders (e.g., stroke, Alzheimer's) with different pathologies and molecular foundations. For instance, it is well-known in Alzheimer's disease that degeneration of the neurons in the nucleus basalis Meynert is observed. However, there is no indication from reading the disclosure that exogenous, loaded monocyte-derived cells are capable of being directed to the site of the lesion and releasing the compound of interest in sufficient quantities to produce some positive and meaningful effect.

4) The disclosure fails to provide adequate guidance pertaining to the ability of "loaded" monocytes to release suitable quantities of the therapeutic agent at the site of interest. As noted in the preceding portions, the claimed invention requires that the monocytes of interest be targeted to the damaged tissue site and release corrective agents in sufficient quantities to provide a

therapeutic effect. Considering the uncertainty of the prior art, the skilled artisan would reasonably conclude that it is extremely unlikely that the claimed monocytes could be directed to the tissue of interest and be capable of releasing sufficient quantities of the therapeutic compound of interest. Nothing in the disclosure suggests that applicants are capable of producing monocytes that can release sufficient quantities of the therapeutic compound at the target site of interest for sufficient periods of time to induce a meaningful therapeutic response.

5) It is well-known in the prior art that many of the mechanisms modulating disease progression in the targeted pathologies remain to be elucidated (Martin, 1995). Thus, it is difficult to see how the claimed invention will treat a disorder when the molecular basis and suitable treatments for that disorder remain to identified.

6) The disclosure fails to provide any working embodiments pertaining to the claimed therapeutic or diagnostic applications. Considering the scope of the claims and unpredictability of the prior art, working embodiments would be required to support the claimed invention. The only example provided in the specification does not represent an art-recognized model for any of the claimed human pathologies (rat lesions were induced using kanaic acid leading to neuronal depletion within a few hours). However, this model does not reproduce any of the clinical symptoms associated with the sundry list of CNS disorders.

7) The prior art discloses a number of concerns pertaining to the use of different vehicles for the delivery of therapeutic agents (Martin, 1995; Parrish *et al.*, 1996; Bankiewicz *et al.*, 1997; Zlokovic and Apuzzo, 1997A; Zlokovic and Apuzzo, 1997B; Kordower, 2003; Furlan *et al.*, 2003; Sikorski and Lesniak, 2005). For instance, Parrish *et al.* (1996) performed studies involving the

recruitment of macrophages to damaged muscle. However, the authors identified a number of caveats (see Discussion, pp. 15 and 16) that preclude the application of this technology to the clinic. Representative caveats included the sequestration of monocytes in the liver and lung (thereby preventing sufficient numbers from reaching the target tissue) and the inability to provide long-term recruitment of "loaded" monocytes such that a therapeutic response could be effected. Additional studies by Martin (1995) concluded that "replacement of defective genes in postmitotic neurons is unlikely to be possible in the near future." Furlan *et al.* (2003) reviewed the results of an *ex vivo* therapeutic approach to treat CNS disorders and concluded that "Unfortunately, several drawbacks limit the applicability of this approach" including reguating the timing and level of gene delivery and expression. A recent review by Sikorski and Lesniak (2005) concluded that "therapies for the treatment of malignant glioma have failed to make appreciable gains regarding patient outcome in the last decade". Some of the problems associated with treating the CNS include the presence of a blood-brain barrier (BBB), lack of organized lymphoid tissue or drainage, paucity of MHC expression in brain parenchyma, and the presence of immunoregulatory factors. Zlokovic and Apuzzo (1997) examined some of the problems associated with various therapeutic approaches to treating CNS disorders and concluded that "Numerous studies on cellular systems and in animal models have revealed a great potential of gene therapy for brain disorders but have also identified major issues that remain to be resolved in clinical reality, such as delivery of genetic material, regulation of the cellular expression of the transgene, efficacy, and selectivity. The negatives associated with the concepts of gene therapy, in addition to the delivery that probably remains a major obstacle, are transient gene expression, toxicity of viral proteins,

drawbacks of antisense therapy, and the problem of immune response to the transfected protein. In addition to these, the problem of extrapolating the cellular work to animals and the animal work to humans cannot be ignored." Moreover, in CNS diseases that result in neuronal cell death, it is not readily manifest that an *ex vivo* monocyte-derived cell approach would be feasible since neuronal regeneration is not feasible at this point in time.

8) The claims are of excessive breadth and are clearly not supported by the disclosure. The claims are broadly directed toward the treatment of any CNS lesion. However, in the absence of further guidance and suitable working embodiments, the all-encompassing breadth of the claimed invention is clearly unsupported and inappropriate.

When the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

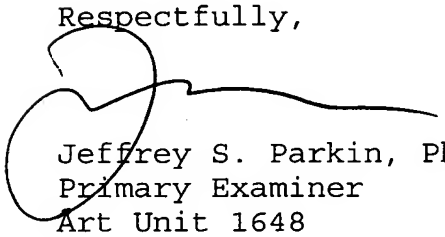
Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces

all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

26 September, 2006